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2. Patent application number <i>(The Patent Office will fill in this part)</i>	0216382.2	01/7700 0.00-0216382.2
3. Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	AstraZeneca AB S-151 85 Sodertalje Sweden	
Patents ADP number <i>(if you know it)</i>	7822448003	
If the applicant is a corporate body, give the country/state of its incorporation	Sweden	
4. Title of the invention	COMPOUNDS	
5. Name of your agent <i>(if you have one)</i>	Margareta Linderoth	
"Address for service" in the United Kingdom to which all correspondence should be sent <i>(including the postcode)</i>	AstraZeneca UK Limited Global Intellectual Property Mereside, Alderley Park Macclesfield Cheshire SK10 4TG	
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Description 43

Claim(s) 04

Abstract

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COMPOUNDS

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well
5 as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes and are particularly effective as inhibitors of TNF (Tumour Necrosis Factor). Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes
10 have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprodysin
15 or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

20 Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of
25 biologically important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many disease conditions. Inhibition of
30 the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis),

inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease)); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated
5 with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis.

10 A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting TACE. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

15 TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) Nature 385:729-733; M.L. Moss *et al.* (1997) Nature 385:733-736] is a member of the admalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNF α , a 26kDa membrane bound protein to release 17kDa biologically active soluble TNF α . [Schlondorff *et al.* (2000) Biochem. J. 347: 131-138]. TACE mRNA is
20 found in most tissues, however TNF α is produced primarily by activated monocytes, macrophages and T lymphocytes. TNF α has been implicated in a wide range of pro-inflammatory biological processes including induction of adhesion molecules and chemokines to promote cell trafficking, induction of matrix destroying enzymes, activation of fibroblasts to produce prostaglandins and activation of the immune system [Aggarwal *et al* (1996) Eur.

25 Cytokine Netw. 7: 93-124]. Clinical use of the anti-TNF biologicals has shown TNF α to play an important role in a range of inflammatory diseases including rheumatoid arthritis, Crohn's disease and psoriasis [Onrust *et al* (1998) Biodrugs 10: 397-422, Jarvis *et al* (1999) Drugs 57:945-964]. TACE activity has also been implicated in the shedding of other membrane bound proteins including TGF α , p75 & p55 TNF receptors, L-selectin and amyloid precursor
30 protein [Black (2002) Int. J. Biochem. Cell Biol. 34: 1-5]. The biology of TACE inhibition has recently been reviewed and shows TACE to have a central role in TNF α production and selective TACE inhibitors to have equal, and possibly greater, efficacy in the collagen

induced arthritis model of RA than strategies that directly neutralise TNF α [Newton et al (2001) Ann. Rheum. Dis. 60: iii25-iii32].

A TACE inhibitor might therefore be expected to show efficacy in all disease where TNF α has been implicated including, but not limited to, inflammatory diseases including 5 rheumatoid arthritis and psoriasis, autoimmune diseases, allergic/atopic diseases, transplant rejection and graft versus host disease, cardiovascular disease, reperfusion injury, malignancy.

WO 99/24399 discloses compounds that are useful as therapeutic agents by virtue of having MMP and TNF inhibitory activity.

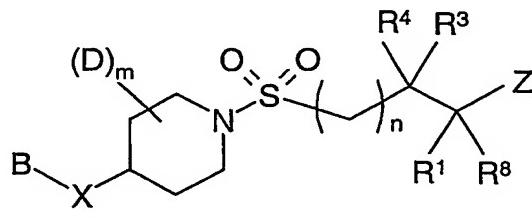
WO 99/38843 discloses compounds useful in the treatment of cancer, inflammation 10 and other conditions associated with matrix metalloproteinases or that are mediated by TNF α or enzymes involved in the shedding of L-selectin, CD23, the TNF receptors, IL-1 receptors or IL-6 receptors.

EP. 1109787 discloses compounds useful in the inhibition of metalloproteinases. These compounds are of particular interest in inhibiting MMP-13 as well as MMP-9.

15 We are able to provide further compounds that have metalloproteinase inhibitory activity, and are in particular inhibitors of TACE (ADAM17).

According to one aspect of the present invention there is provided compounds of the formula (1):

20



wherein Z is selected from $-\text{CONR}^{15}\text{OH}$ and $-\text{N}(\text{OH})\text{CHO}$;

25 R^{15} is hydrogen or $\text{C}_{1-3}\text{alkyl}$;

wherein R^1 is hydrogen or a group selected from $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, $\text{C}_{3-7}\text{cycloalkyl}$, $\text{C}_{5-7}\text{cycloalkenyl}$, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano,

trifluoromethyl, trifluoromethoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₃₋₆cycloalkyl (optionally substituted by one or more R¹⁷), aryl (optionally substituted by one or more R¹⁷), heteroaryl (optionally substituted by one or more R¹⁷), heterocyclyl, C₁₋₄alkoxycarbonyl, —OR⁵, —SR², —SOR², —SO₂R², —COR², —CO₂R⁵, —CONR⁵R⁶, —NR¹⁶COR⁵, —SO₂NR⁵R⁶ and —NR¹⁶SO₂R²;

R¹⁶ is hydrogen or C₁₋₃alkyl;

R¹⁷ is selected from halo, C₁₋₆alkyl, C₃₋₆cycloalkyl and C₁₋₆alkoxy;

10

R² is group selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₅₋₇cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC₁₋₄alkyl and heteroarylC₁₋₄alkyl where the group is optionally substituted by one or more halo;

15 R⁵ is hydrogen or a group selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₅₋₇cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, arylC₁₋₄alkyl and heteroarylC₁₋₄alkyl where the group is optionally substituted by one or more halo;

R⁶ is hydrogen, C₁₋₆alkyl or C₃₋₆cycloalkyl;

20

or R⁵ and R⁶ together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

wherein R⁸ is hydrogen or a group selected from C₁₋₆alkyl, C₃₋₇cycloalkyl and heterocyclyl

25 where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy and C₁₋₄alkyl;

or R¹ and R⁸ together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

30 wherein R³ and R⁴ are independently hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₅₋₇cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

wherein m is 0 or 1;

wherein D is hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl or fluoro;

5

wherein X is -(CR⁹R¹⁰)—Q—(CR¹¹R¹²)u— where u is 0 or 1;

Q is O, S, SO or SO₂;

10 R⁹, R¹⁰, R¹¹ and R¹² are independently selected from hydrogen, C₁₋₄alkyl and C₃₋₆cycloalkyl;

wherein B is C₂₋₄alkenyl or C₂₋₄alkynyl, each being optionally independently substituted by a group selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heterocyclyl whereby the group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl,

15 trifluoromethoxy, —CONHR¹³, —CONHR¹³R¹⁴, —SO₂R¹³, —SO₂NHR¹³, —SO₂NR¹³R¹⁴, —NHSO₂R¹³, C₁₋₄alkyl and C₁₋₄alkoxy.

R¹³ and R¹⁴ are independently hydrogen, C₁₋₄alkyl or C₃₋₅cycloalkyl;

20 or R¹³ and R¹⁴ together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt thereof.

25 It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses metalloproteinases inhibition activity and in particular TACE inhibition activity. The synthesis of optically active forms may be carried out by standard
30 techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Compounds of formula (1) are therefore provided as enantiomers, diastereomers, geometric isomers and atropisomers.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings 5 within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has metalloproteinases inhibition activity and in particular TACE inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be 10 understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have 15 metalloproteinases inhibition activity and in particular TACE inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess metalloproteinases inhibition activity and in particular TACE inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore 20 defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such 25 salts. Such acid addition salts include but are not limited to hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where the compounds of formula (1) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for 30 example triethylamine or tris-(2-hydroxyethyl)amine

The compounds of formula (1) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy

group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

- 5 Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example
10 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give
15 the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C₁₋₁₀alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C₁₋₁₀alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C₁₋₄)alkylcarbamoyl and N-(di-(C₁₋₄)alkylaminoethyl)-N-
20 (C₁₋₄)alkylcarbamoyl (to give carbamates); di-(C₁₋₄)alkylaminoacetyl and carboxyacetyl.
Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C₁₋₄)alkylaminomethyl and di-((C₁₋₄)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in-vivo* hydrolysable esters include, for example, R^AC(O)O(C₁₋₆)alkyl-
25 CO-, wherein R^A is for example, benzyloxy-(C₁₋₄)alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C₁₋₄)piperazino-(C₁₋₄)alkyl, piperazino-(C₁₋₄)alkyl and morpholino-(C₁₋₄)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and
30 branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example,

"C₁₋₃alkyl" includes methyl, ethyl, propyl and isopropyl, examples of "C₁₋₄alkyl" include the examples of "C₁₋₃alkyl", butyl and *t*-butyl and examples of "C₁₋₆alkyl" include the examples of "C₁₋₄alkyl" and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. Examples of "C₁₋₂₀alkyl" include the examples of "C₁₋₆alkyl" and other straight chain and branched alkyl groups. An analogous convention applies to other generic terms, for example "C₂₋₄alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C₂₋₆alkenyl" include the examples of "C₂₋₄alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C₂₋₄alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of "C₂₋₆alkynyl" include the examples of "C₂₋₄alkynyl" and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term "C₃₋₆cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "C₃₋₇cycloalkyl" includes "C₃₋₆cycloalkyl" and additionally cycloheptyl. The term "C₃₋₁₀cycloalkyl" includes "C₃₋₇cycloalkyl" and additionally cyclooctyl, cyclononyl and cyclodecyl.

"Heterocycloalkyl" is a monocyclic saturated 3- to 10-membered ring containing 1 or 2 heteroatoms selected from nitrogen, sulphur or oxygen wherein a ring nitrogen or sulphur may be oxidised to the N-oxide or S-oxide(s).

"C₅₋₇cycloalkenyl" is a monocyclic 5 to 7-membered ring containing 1, 2 or 3 double bonds. Examples are cyclopentenyl and cyclohexenyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C₁₋₄alkoxy" include methoxy, ethoxy, propoxy and isopropoxy.

Examples of "C₁₋₆alkoxy" include the examples of "C₁₋₄alkoxy" and additionally pentyloxy, 1-ethylpropoxy and hexyloxy. Examples of "C₁₋₄alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and isopropoxycarbonyl.

Examples of "aryl" are phenyl and naphthyl.

Examples of "arylC₁₋₄alkyl" are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

"Heteroaryl" is monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen may be oxidised. Examples of heteroaryl are pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Preferably heteroaryl is pyridyl, imidazolyl, quinolinyl, pyrimidinyl, thienyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl.

Examples of "heteroarylC₁₋₄alkyl" are pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, quinolinylpropyl and oxazolylmethyl.

- "Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring containing 4 to 12 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)-; a ring nitrogen or sulphur atom may be optionally oxidised to form the N-oxide or S-oxide(s); and a ring -NH may be optionally substituted by acetyl, formyl, methyl or mesyl. Examples and suitable values of the term "heterocyclyl" are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylypiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-2*H*-pyranyl, tetrahydrofuranyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxybenzyl. Preferred values are 3,4-dihydro-2*H*-pyran-5-yl, tetrahydrofuran-2-yl, 2,2-dimethyl-1,3-dioxolan-2-yl and 3,4-dimethylenedioxybenzyl.
- 15 Heterocyclic rings are rings containing 1, 2 or 3 rings atoms selected nitrogen, oxygen and sulphur. "Heterocyclic 5 to 7-membered" rings are pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, thiomorpholinyl, thiopyranyl and morpholinyl. "Heterocyclic 4 to 7-membered" rings include the examples of "heterocyclic 5 to 7-membered" and additionally azetidinyl.
- 20 "Saturated heterocyclic 3 to 6-membered" rings are oxiranyl, aziridinyl, thiirane azetidinyl, oxetanyl, thietanyl, tetrahydrothienyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2*H*-pyranyl, tetrahydro-2*H*-thiopyranyl and piperidinyl and a ring nitrogen may be substituted by a group selected from formyl, acetyl and mesyl.
- 25 A "carbocyclic 3 to 6-membered" ring is a saturated, partially saturated or unsaturated ring containing 3 to 6 ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopent-3-enyl, cyclohexyl and cyclopent-2-enyl.

- Where optional substituents are chosen from "one of more" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.
- 30 Preferably "one or more" means "1, 2 or 3" and this is particularly the case when the group or substituent is halo. "One or more" may also mean "1 or 2".

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 5.09).

Preferred values of Z, R¹, R³, R⁴, R⁸, n, m, D, X and B are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

5

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein Z is -CONR¹⁵OH.

In another aspect of the invention Z is -N(OH)CHO.

10

In one aspect of the invention R¹⁵ is hydrogen, methyl, ethyl or isopropyl.

In another aspect R¹⁵ is hydrogen.

In one aspect of the invention R¹ is hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₅₋₇cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is 15 optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl (optionally substituted by R¹⁷), aryl (optionally substituted by R¹⁷), heteroaryl (optionally substituted by R¹⁷), C₁₋₄alkoxycarbonyl, -OR⁵, -SR², -SOR², -SO₂R², -COR², -CO₂R⁵, -CONR⁵R⁶, -NR¹⁶COR⁵, -SO₂NR⁵R⁶ and -NR¹⁶SO₂R².

20 In another aspect of the invention R¹ is hydrogen, C₁₋₆alkyl or aryl where C₁₋₆alkyl or aryl are optionally substituted by one or more substituents independently selected from C₁₋₄alkyl, aryl (optionally substituted by R¹⁷) and heteroaryl (optionally substituted by R¹⁷).

In another aspect of the invention R¹ is methyl, ethyl, propyl or phenyl optionally substituted by phenyl or pyrimidinyl.

25 In a further aspect of the invention R¹ is methyl, phenyl, phenethyl or pyrimidin-2-ylpropyl.

In one aspect of the invention R¹⁶ is hydrogen, methyl or ethyl.

In another aspect R¹⁶ is methyl or ethyl.

30 In another aspect of the invention R¹⁶ is hydrogen.

In one aspect of the invention R¹⁷ is halo or C₁₋₄alkyl.

In another aspect R¹⁷ is fluoro, chloro, bromo or methyl.

In another aspect of the invention R¹⁷ is fluoro or methyl.

In one aspect of the invention R² is a group selected from C₁₋₆alkyl, aryl and arylC₁₋₄alkyl where the group is optionally substituted by halo.

5 In another aspect R² is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R² is methyl.

In one aspect of the invention R⁵ is hydrogen or a group selected from C₁₋₆alkyl, aryl 10 and arylC₁₋₄alkyl where the group is optionally substituted by halo.

In another aspect R⁵ is hydrogen or a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R⁸ is hydrogen, methyl, ethyl, propyl or isopropyl.

15 In another aspect R⁸ is hydrogen.

In one aspect of the invention R³ is hydrogen.

In one aspect of the invention R⁴ is hydrogen.

20

In one aspect of the invention n is 0.

In another aspect n is 1.

In one aspect of the invention m is 0.

25 In another aspect of the invention m is 1.

In one aspect of the invention D is hydrogen, methyl or fluoro.

In another aspect D is hydrogen.

30 In one aspect of the invention X is -CR⁹R¹⁰-Q- or -CR⁹R¹⁰-Q-CR¹¹R¹²-.

In another aspect of the invention X is -(CH₂)-Q- or -(CH₂)-Q-(CH₂)-.

In a further aspect of the invention X is -(CH₂)-O- or -(CH₂)-O-(CH₂)-.

In one aspect of the invention u is 1.

In another aspect u is 0.

In one aspect of the invention Q is O.

5

In one aspect of the invention R⁹ is hydrogen.

In one aspect of the invention R¹⁰ is hydrogen.

10 In one aspect of the invention R¹¹ is hydrogen.

In one aspect of the invention R¹² is hydrogen.

In one aspect of the invention B is C₂₋₄alkenyl or C₂₋₄alkynyl, each being optionally independently substituted by C₁₋₄alkyl, C₃₋₆cycloalkyl or heterocycloalkyl. In one aspect of the invention B is vinyl or ethynyl where each is optionally independently substituted by methyl or ethyl.

In a further aspect B is vinyl, ethynyl, prop-1-enyl, prop-1-ynyl or but-1-ynyl.

20 A preferred class of compound is of the formula (1) wherein:

Z is -N(OH)CHO;

R¹ is hydrogen or a group selected from C₁₋₆alkyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₅₋₇cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl,

25 trifluoromethoxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl (optionally substituted by R¹⁷), aryl (optionally substituted by R¹⁷), heteroaryl (optionally substituted by R¹⁷), C₁₋₄alkoxycarbonyl, -OR⁵, -SR², -SOR², -SO₂R², -COR², -CO₂R⁵, -CONR⁵R⁶, -NR¹⁶COR⁵, -SO₂NR⁵R⁶ and -NR¹⁶SO₂R²;

R¹⁶ is hydrogen, methyl or phenyl;

30 R¹⁷ is halo or C₁₋₄alkyl;

R² is a group selected from C₁₋₆alkyl, aryl and arylC₁₋₄alkyl where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from C_{1-6} alkyl, aryl and aryl C_{1-4} alkyl where the group is optionally substituted by halo;

R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

5 n is 0;

 m is 1;

 D is hydrogen, methyl or fluoro;

 X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

 B is C_{2-4} alkenyl or C_{2-4} alkynyl, each being optionally independently substituted by C_{1-4}

10 alkyl or C_{3-6} cycloalkyl.

Another preferred class of compound is of the formula (1) wherein:

Z is $-N(OH)CHO$;

R^1 is hydrogen, C_{1-6} alkyl or aryl where C_{1-6} alkyl or aryl are optionally substituted by

15 one or more substituents independently selected from C_{1-4} alkyl, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17});

R^{17} is halo or C_{1-4} alkyl;

R^3 is hydrogen;

R^4 is hydrogen;

20 n is 0;

 m is 1;

 D is hydrogen, methyl or fluoro;

 X is $-(CH_2)-O-$ or $-(CH_2)-O-(CH_2)-$; and

 B is C_{2-4} alkenyl or C_{2-4} alkynyl, each being optionally independently substituted by C_{1-4}

25 alkyl or C_{3-6} cycloalkyl.

Another preferred class of compound is of the formula (1) wherein:

Z is $-CONR^{15}OH$;

R^1 is hydrogen or a group selected from C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{5-7}

30 cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{3-6} cycloalkyl (optionally substituted by R^{17}), aryl (optionally substituted by R^{17}), heteroaryl (optionally substituted by R^{17}), C_{1-4} alkoxycarbonyl,

$-\text{OR}^5$, $-\text{SR}^2$, $-\text{SOR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{COR}^2$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^5\text{R}^6$, $-\text{NR}^{16}\text{COR}^5$, $-\text{SO}_2\text{NR}^5\text{R}^6$ and $-\text{NR}^{16}\text{SO}_2\text{R}^2$;

R^{15} is hydrogen, methyl, ethyl or isopropyl;

R^{16} is hydrogen, methyl or phenyl;

5 R^{17} is halo or $\text{C}_{1-4}\text{alkyl}$;

R^2 is a group selected from $\text{C}_{1-6}\text{alkyl}$, aryl and $\text{arylC}_{1-4}\text{alkyl}$ where the group is optionally substituted by halo;

R^5 is hydrogen or a group selected from $\text{C}_{1-6}\text{alkyl}$, aryl and $\text{arylC}_{1-4}\text{alkyl}$ where the group is optionally substituted by halo;

10 R^3 is hydrogen, methyl, ethyl or phenyl;

R^4 is hydrogen, methyl, ethyl or phenyl;

n is 0;

m is 1;

D is hydrogen, methyl or fluoro;

15 X is $-(\text{CH}_2)-\text{O}-$ or $-(\text{CH}_2)-\text{O}-(\text{CH}_2)-$; and

B is $\text{C}_{2-4}\text{alkenyl}$ or $\text{C}_{2-4}\text{alkynyl}$, each being optionally independently substituted by $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$.

Another preferred class of compound is of the formula (1) wherein:

20 Z is $-\text{CONR}^{15}\text{OH}$;

R^1 is hydrogen, $\text{C}_{1-6}\text{alkyl}$ or aryl where $\text{C}_{1-6}\text{alkyl}$ or aryl are optionally substituted by one or more substituents independently selected from $\text{C}_{1-4}\text{alkyl}$, aryl (optionally substituted by R^{17}) and heteroaryl (optionally substituted by R^{17});

R^{17} is halo or $\text{C}_{1-4}\text{alkyl}$;

25 R^{15} is hydrogen, methyl, ethyl or isopropyl

R^3 is hydrogen;

R^4 is hydrogen;

n is 0;

m is 1;

30 D is hydrogen, methyl or fluoro;

X is $-(\text{CH}_2)-\text{O}-$ or $-(\text{CH}_2)-\text{O}-(\text{CH}_2)-$; and

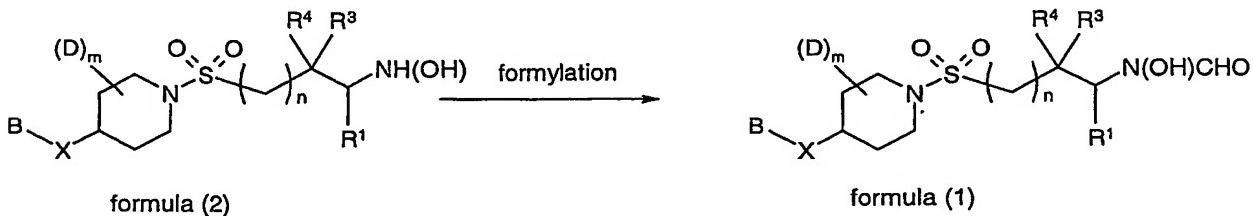
B is $\text{C}_{2-4}\text{alkenyl}$ or $\text{C}_{2-4}\text{alkynyl}$, each being optionally independently substituted by $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-6}\text{cycloalkyl}$.

In another aspect of the invention, preferred compounds of the invention are any one of:

- (1-phenyl-2-{[4-(prop-2-nyloxy)piperidin-1-yl]sulfonyl}ethyl)hydroxyformamide;
- 5 2-{[4-(allyloxy)piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;
- 2-{[4-[but-2-enyloxy]piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;
- 2-{[4-(but-2-nyloxy)piperidin-1-yl]sulfonyl}-1-phenylethyl(hydroxy)formamide;
- (2-{[4-(pent-2-nyloxy)piperidin-1-yl]sulfonyl}-1-phenylethyl)hydroxyformamide;
- 10 1-({[4-(but-2-nyloxy)piperidin-1-yl]sulfonyl}methyl)-3-phenylpropyl(hydroxy)formamide;
- 2-{[4-(but-2-nyloxy)piperidin-1-yl]sulfonyl}-1-methylethyl(hydroxy)formamide;
- 1-({[4-(but-2-nyloxy)piperidin-1-yl]sulfonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide;
- 1-[{[4-[(but-2-nyloxy)methyl]piperidin-1-yl]sulfonyl}methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide; and
- 15 2-{[4-[(but-2-nyloxy)methyl]piperidin-1-yl]sulfonyl}-1-methylethyl(hydroxy)formamide.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is $-\text{N}(\text{OH})\text{CHO}$, which process comprises the steps of:

- converting a hydroxylamine of formula (2) into a compound of formula (1);



Scheme 1

25

and thereafter if necessary:

- converting a compound of the formula (1) into another compound of the formula (1);
- removing any protecting groups;
- forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

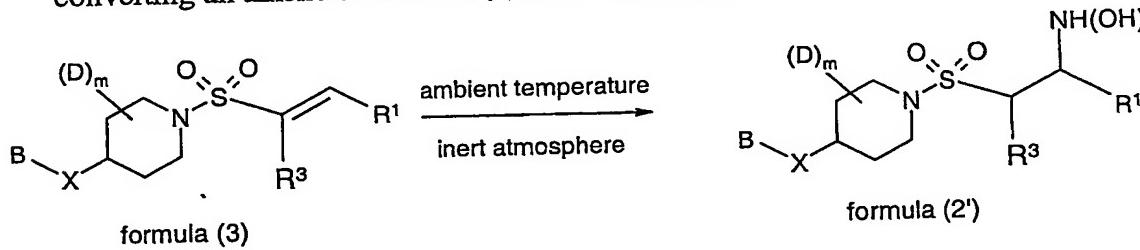
Formylation may be suitably performed by adding a preformed mixture of acetic acid (8 equivalents) and formic acid (excess) to formula (2) in THF or DCM and stirring the solution for 15h at temperatures ranging from 0°C to room temperature followed by stirring in methanol. Alternatively a formylation method described in *J.Med.Chem.*, 2002, 45, 219 using trifluoroethylformate can be used.

This process may further comprise a process for the preparation of a hydroxylamine of formula (2'):

- when n is 0 and R⁴ is hydrogen (indicated as a compound of formula (2')), which

process comprises:

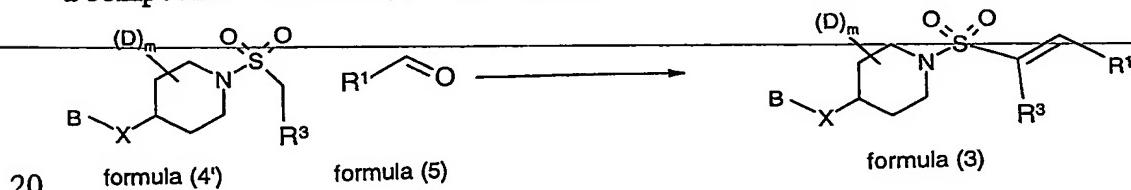
- b) converting an alkene of formula (3) into a hydroxylamine of formula (2');



Scheme 2

Suitable reagents for such a conversion include aqueous hydroxylamine in THF under an argon atmosphere.

The alkene of formula (3) can be prepared by the reaction of a compound of formula (4') with a compound of formula (5) under Wadsworth-Emmons or Peterson reaction conditions;

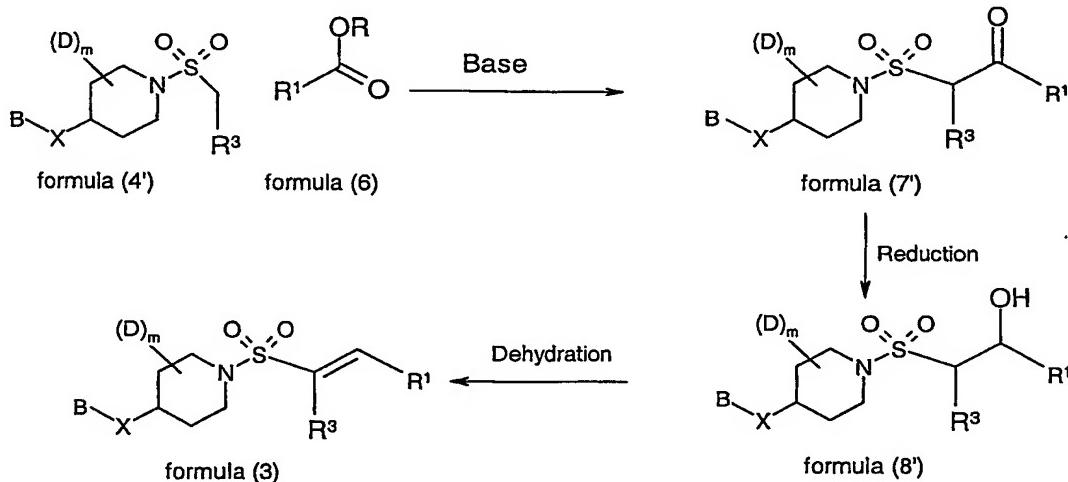


Scheme 3

Wadsworth-Emmons or Peterson reactions involve the forming of the anion of formula (4') with 2 equivalents of lithium bis(trimethylsilyl)amide or sodium hydride or lithium diisopropylamide in THF at temperatures of -78°C to 0°C and reacting this with 1 equivalent of diethylchlorophosphate (Wadsworth Emmons) or 1 equivalent of TMSCl (Peterson). After

1h an aldehyde (1.1 equivalent) in THF is added to the resultant anion described and reacted at room temperature over 15h.

The alkene of formula (3) can also be prepared by the reaction of a compound of formula (4')
5 with a compound of formula (6) as illustrated by scheme 4;



Scheme 4

Suitable bases include LHMDS, NaH or LDA in THF at temperatures of -78°C to 0°C to form
10 the anion.

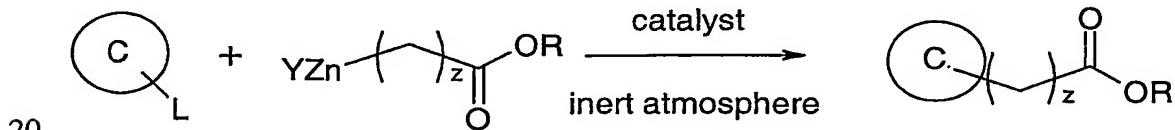
Suitable reducing agents for the reduction step include sodium borohydride in ethanol or borane-dimethylsulphide complex or borane-THF complex in THF at room temperature.

Suitable dehydration reagents or the dehydration step include methanesulphonylchloride or tosylchloride and triethylamine in dichloromethane at room temperature.

15

The present invention provides a process for the preparation of a compound of formula (6) wherein R¹ is C₁₋₆alkyl substituted by aryl or heteroaryl where the aryl and heteroaryl groups are optionally substituted by one or more R¹⁷.

Such a process is outlined in the scheme below:



wherein C is aryl or heteroaryl both being optionally substituted by one or more R¹⁷;
L is a suitable leaving group such as halo, tosyl, mesyl or triflate;

Y is such that a zinc metal salt is formed i.e. Y is for example bromo or iodo; and z is an integer of 1 to 6 such that $()_z$ represents $C_{1-6}\text{alkyl}$; it is to be understood that in this



aspect of the invention R^1 is represented by so that the $C_{1-6}\text{alkyl}$ group represented by $()_z$ may be a straight or branched chain.

- 5 In another aspect of the invention $()_z$ may represent $C_{1-20}\text{alkyl}$.

The reaction is performed under an inert atmosphere, which ensures consistent catalytic activity and in a non-protic solvent such as THF. Suitable catalysts include nickel based and palladium (0) based catalysts. Preferably a palladium (0) based catalyst is used. The palladium (0) based catalyst may be generated from palladium (II) based compounds when

- 10 used in conjunction with a promoter such as PPh_3 .

A specific example of a compound of formula (6) is ethyl 4-(pyrimidin-2-yl)butanoate. This compound is formed by the reaction of 2-bromopyrimidine with 4-ethoxy-4-oxo-butylzinc bromide in the presence of bis(acetonitrile)palladium (II) chloride (2.5mmol) and triphenylphosphine in a non-protic solvent and under an inert atmosphere. The stoichiometric 15 amount of zinc salt produced as a by-product can be removed from the reaction mixture by washing with an aqueous solution of ethylenediamine tetraacetic acid terasodium salt.

Preferably the non-protic solvent is THF.

Preferably the inert atmosphere is a nitrogen atmosphere.

- 20 Or a process for the preparation of a hydroxylamine of formula (2):

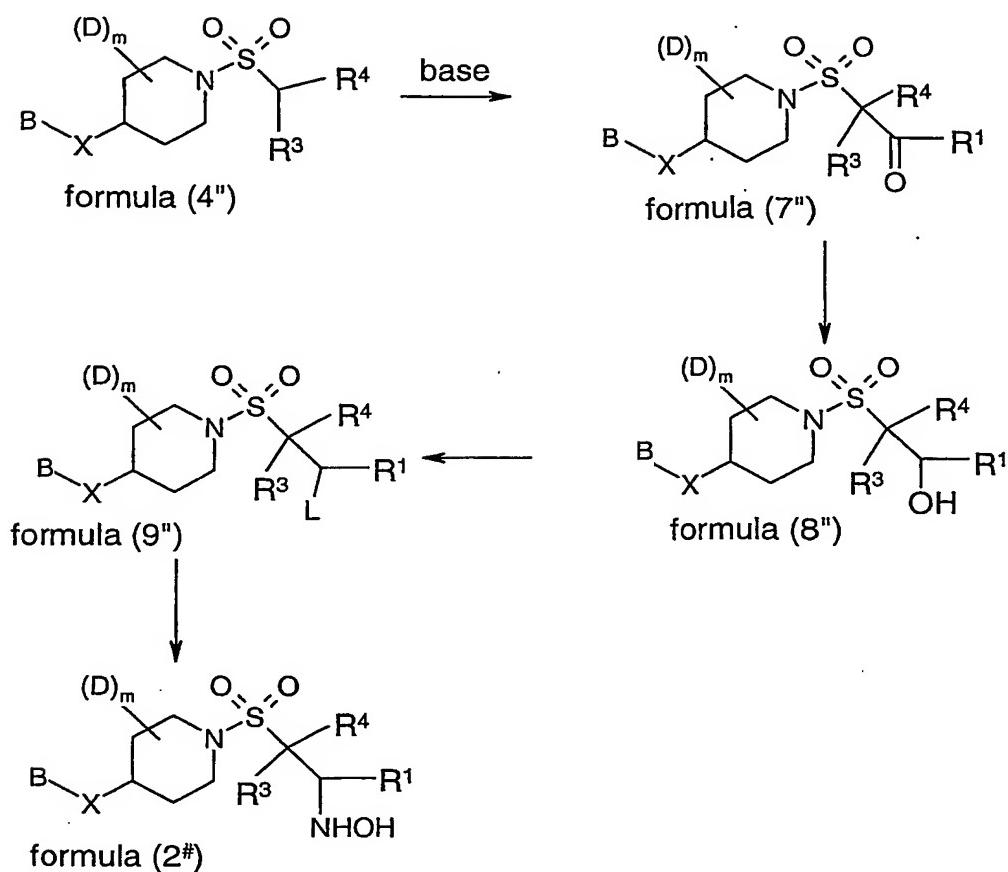
- when n is 0 (indicated as a compound of formula $(2^\#)$) may comprise;

- c) i) reacting a compound of formula (4") (see scheme 10 for its preparation) with

$R^1\text{COOR}$, $R^1\text{COCl}$ or activated $R^1\text{COOR}$ to yield a ketone of formula (7")

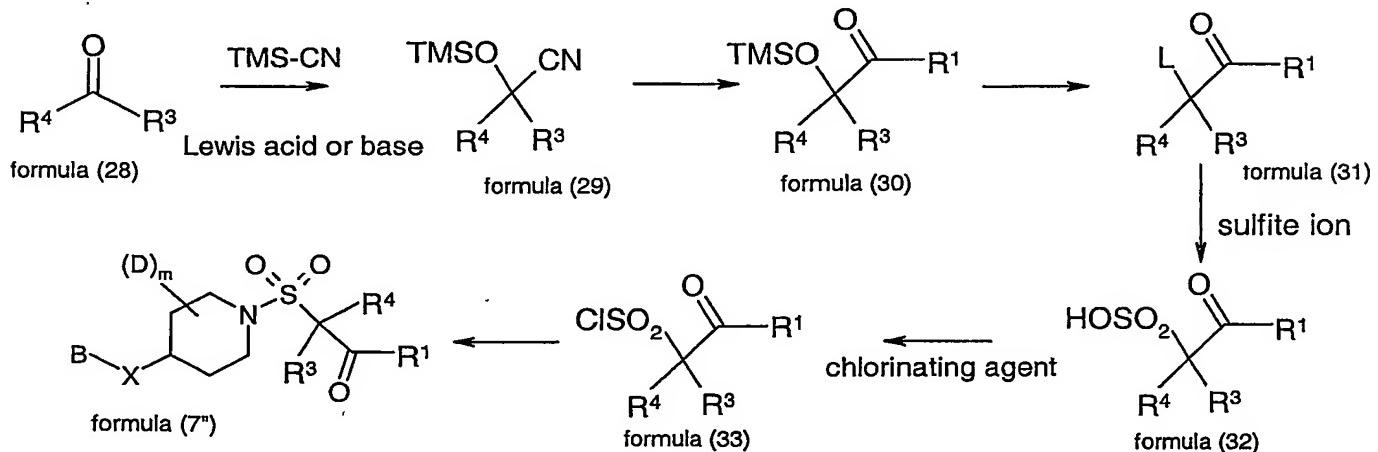
(where R is $C_{1-20}\text{alkyl}$ e.g. methyl, ethyl or aryl $C_{1-4}\text{alkyl}$ e.g.benzyl);

- 25 ii) reducing the ketone of formula (7") to yield an alcohol of formula (8");
 iii) converting -OH group of the alcohol of formula (8") into a leaving group (L)
 such as a halide, mesylate, tosylate etc. (see compound of formula (9"));
 iv) displacing the leaving group with aqueous hydroxylamine to yield a
 hydroxylamine of formula (2#);



Scheme 5

A ketone of formula (7'') may additionally be prepared by the process illustrated in scheme 6:



5

Scheme 6

The silyl group present in the compound of formula (30) can be removed by TBAF.

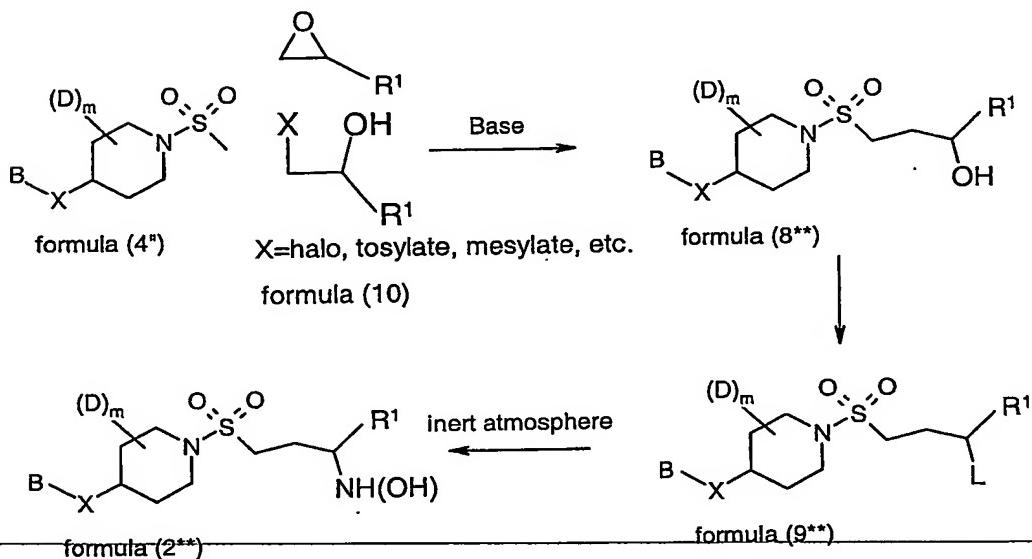
Suitable leaving groups (L) are halo, mesyl and tosyl.

- 10 A suitable chlorinating agent is POCl_3 .

A compound of formula (7'') is prepared in the last stage by reacting the compound of formula (33) with the appropriate piperidine reagent.

Or a process for the preparation of a hydroxylamine of formula (2):

- 5 • when n is 1 and R³ and R⁴ are both hydrogen (indicated as a compound of formula (2**)) may further comprise:
- c) i) reacting a compound of formula (4'') with a compound of formula (10) (either an epoxide or equivalent) to yield an alcohol of formula (8**);
 ii) converting -OH group of the alcohol of formula (8**) into a leaving group such as a halide, mesylate, tosylate etc. (see compound of formula (9**));
 10 iii) displacing the leaving group with aqueous hydroxylamine to yield a hydroxylamine of formula (2**);



15

Scheme 7

Suitable bases are LHMDS and lithium diisopropylamide at temperatures from -78°C to 0°C.

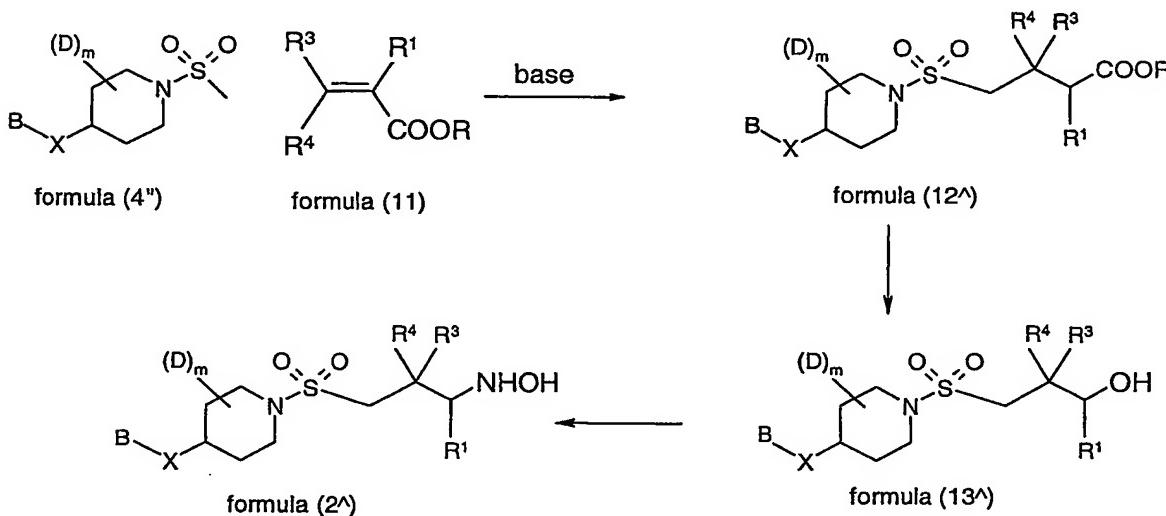
Suitable leaving groups (L) are chloro, bromo, iodo, methanesulphonyl and tosyl and these would be formed from the alcohol by treatment with methanesulphonyl chloride and pyridine

- 20 in DCM (mesylate), tosyl chloride and pyridine in DCM (tosylate), triphenylphosphine and carbon tetrabromide (bromo); the chloro, bromo and iodo derivatives could also be prepared from the mesylate or tosylate by addition of a suitable halide source, e.g. tetrabutylammonium iodide or sodium iodide or lithium chloride in a solvent such as acetone.

Or a process for the preparation of a hydroxylamine of formula (2):

- when n is 1, indicated as a compound of formula (2^Δ), may further comprise:

- d) i) reacting a compound of formula (4'') with a compound of formula (11) to yield
 5 an ester of formula (12^Δ);
 ii) converting the ester of formula (12^Δ) into an alcohol of formula (13^Δ);
 iii) displacing the -OH group with aqueous hydroxylamine to yield a
 hydroxylamine of formula (2^Δ);



10

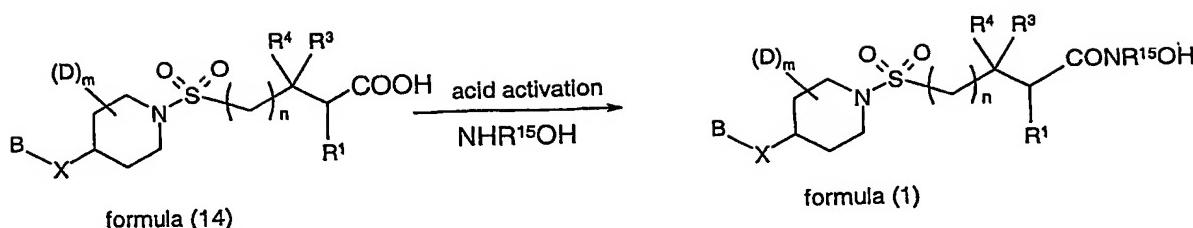
Scheme 8

The group -COOR of formula (12^Δ) is representative of an ester wherein R may be C₁-
 20 alkyl, e.g. methyl, ethyl or arylC₁₋₄alkyl, e.g. benzyl.

Baeyer-Villiger reaction conditions such as a peracid e.g. *m*-CPBA in DCM are suitable for the conversion of the ester group into the alcohol group. It may be appropriate to
 15 convert the alcohol group into a leaving group such as bromo, iodo, mesyl and tosyl, before displacement with aqueous hydroxylamine.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester
 20 thereof wherein Z is -CONR¹⁵OH, which process comprises:

- a) converting an acid of formula (14) into a compound of formula (1);



Scheme 9

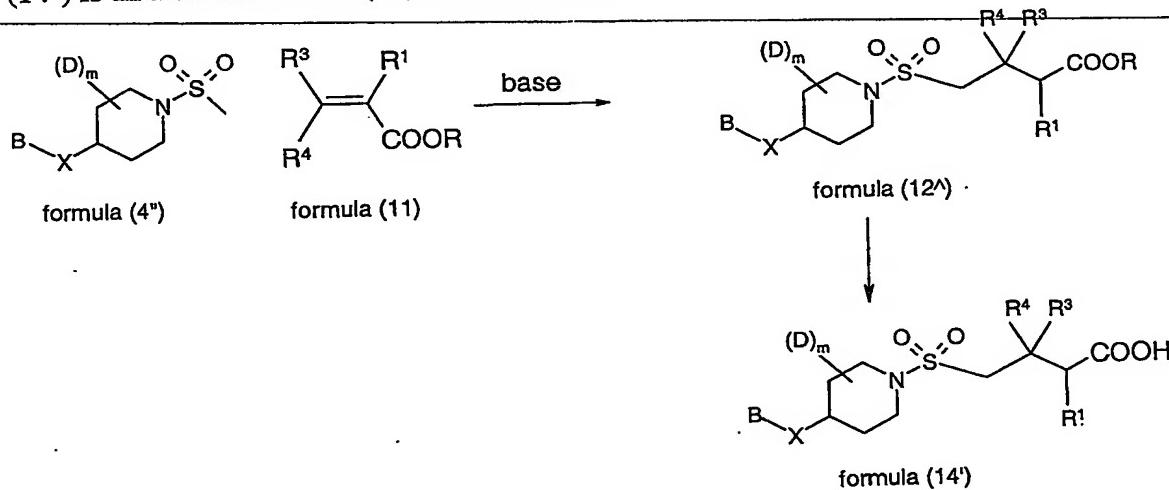
and thereafter if necessary:

- 5 i) converting a compound of the formula (1) into another compound of the formula (1);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

The acid of formula (14) may be suitably activated by conversion to an acid halide, such as the
 10 acid chloride or to an activated ester using carbonyldiimidazole, a carbodiimide or a pentafluorophenyl ester.

Alternatively when the acid of formula (14) is an ester e.g. the methyl or ethyl ester, it can be converted directly to a compound of formula (1) by reaction with NHR^{15}OH .

- 15 Also provided is a process for the preparation of an acid of formula (14) which process comprises;
 - b) reacting a compound of formula (4'') with an alkene of formula (11) to yield an ester of formula (12^a) which is hydrolysed to an acid of formula (14[']) where an acid of formula
- 20 (14[']) is an acid of formula (14) wherein n is 1;

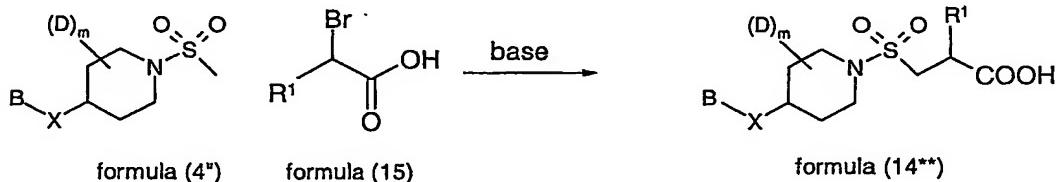


Scheme 10

Suitable bases able to deprotonate a compound of formula (4'') are BuLi, LDA, LHMDS
 5 followed by the addition of a copper salt e.g. CuBr-dimethylsulphide complex, CuI, in
 solvents such as dimethylsulphide, ether, THF at temperatures from -78°C to RT.

Or a process for the preparation of an acid of formula (14) comprises;

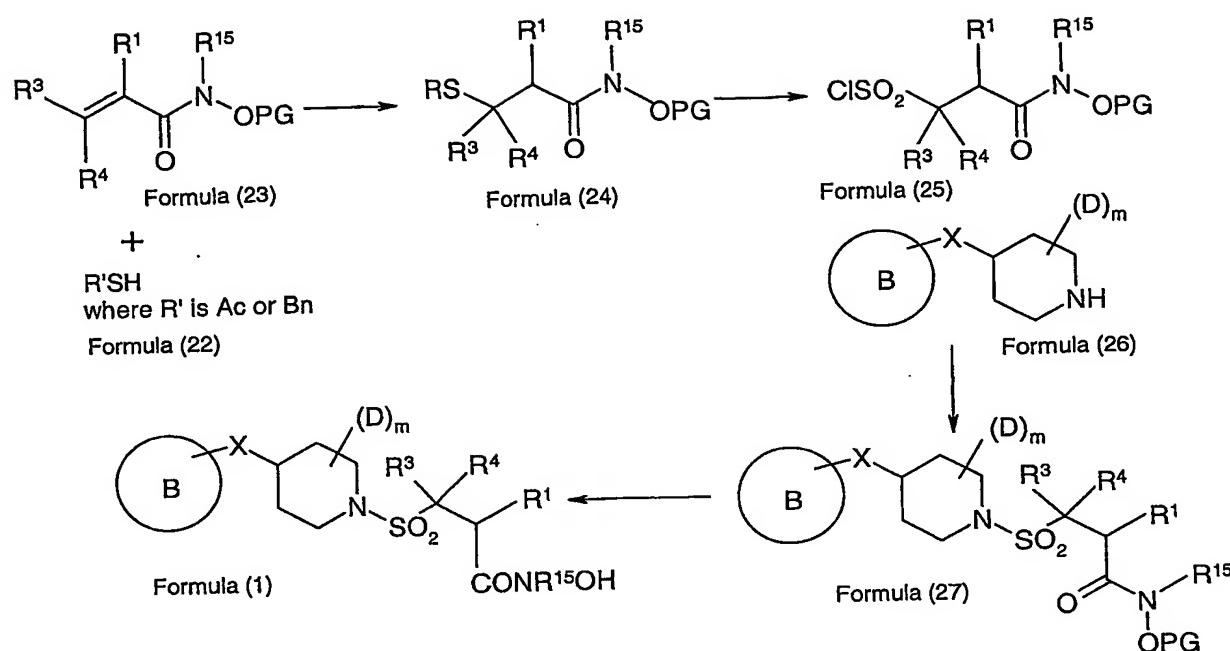
- c) reacting a compound of formula (4'') with a compound of formula (15) to yield an acid
 10 of formula (14**) which is an acid of formula (14) wherein n is 0, R³ is hydrogen and R⁴ is
 hydrogen;



Scheme 11

Suitable bases to deprotonate formula (4'') include LHMDS, LDA, NaH in solvents such as
 15 THF, Ether at temperatures from -78°C to 0°C.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Z is -CONR¹⁵OH and n is 0, which process comprises steps as outlined in
 20 scheme 12:



Scheme 12

The process of scheme 12 comprises the steps of:

- a) reacting a thiol of formula (22) with an acrylate of formula (23) at temperatures of 5 0°C to 70°C to yield a thioether of formula (24);
- b) oxidising the thioether of formula (24) to a sulfonyl chloride of formula (25) by bubbling chlorine gas onto a solution of the thioether in acetic acid at temperatures of 0°C to room temperature;
- c) reacting the sulfonyl chloride of formula (25) with a piperidine of formula (26) under standard sulfonamide conditions (e.g. triethylamine in DCM at temperatures from 0°C to 50°C) to yield a compound of formula (27);
- d) removing the protecting group to yield a compound of formula (1).

The protecting group (PG) may be benzyl- or 2,4-dimethoxybenzyl-. The former can be removed by treatment with hydrogen/ palladium and the latter by treatment with mild acid (see Tetrahedron Letters, 1998m 39(43), 7865).

The process of scheme 12 may further comprise if necessary:

- i) converting a compound of the formula (1) into another compound of the formula (1);
- ii) removing any other protecting groups;
- 20 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

In another aspect of the invention, there is provided a process for the preparation of a compounds of formula (4), formula (4') and formula (4'') which process comprises;

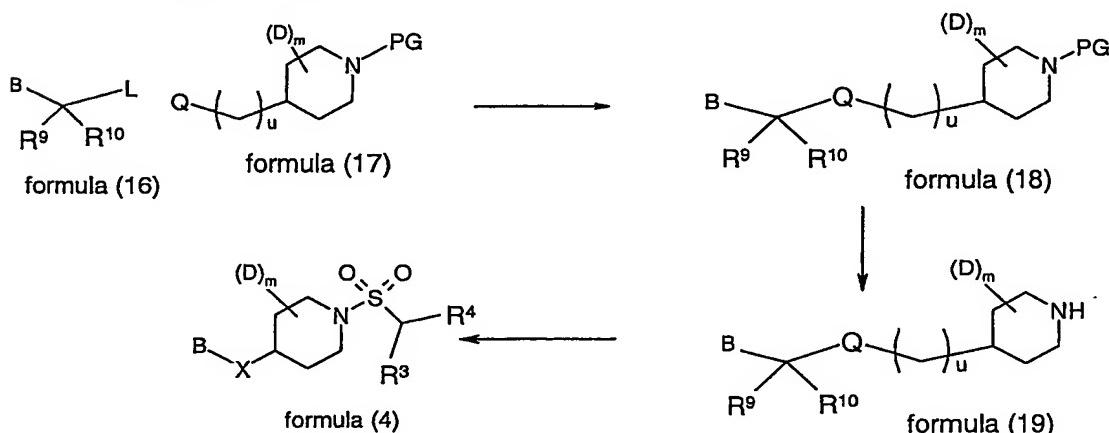
- 5 a) reacting a compound of formula (16) with a compound of formula (17) (wherein Q is not oxidised), in the presence of a base to deprotonate the compound of formula (17), to yield a compound of formula (18);

b) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.

c) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})_t-Q-(CR^{11}R^{12})_u$; and

10 d) oxidising Q as required.

When R^4 is hydrogen a compound of formula (4') is produced and when R^3 and R^4 are both hydrogen compound of formula (4'') is produced



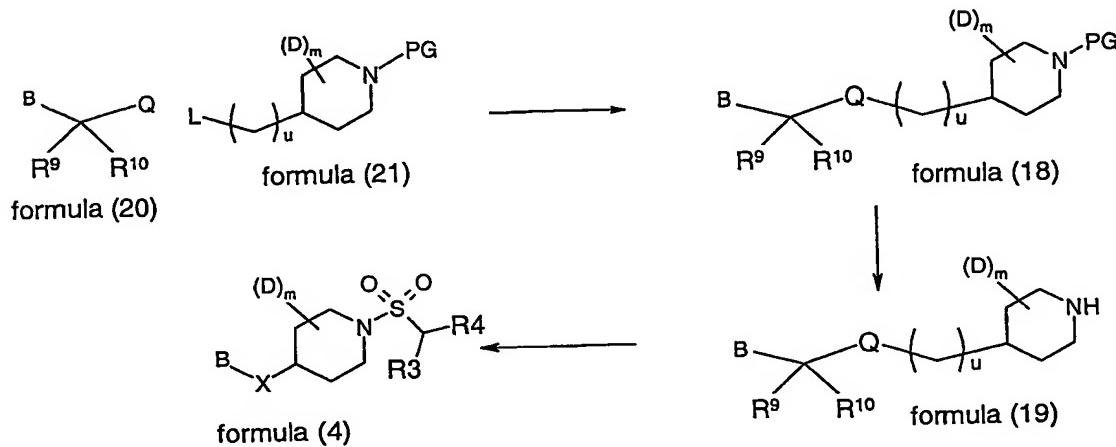
Scheme 13

Compounds of formula (4), formula (4') and formula (4'') may also be prepared by a process which comprises;

- 20 e) reacting a compound of formula (20) (wherein Q is not oxidised) with a compound of formula (21), in the presence of a base to yield a compound of formula (18);
f) removing the protecting group (PG) from the compound of formula (18) to yield a compound of formula (19);.
g) reacting the compound of formula (19) with a suitable reagent to yield a compound of formula (4) wherein X is $-(CR^9R^{10})_n-Q-(CR^{11}R^{12})_m$; and
25

h) oxidising Q as required.

When R⁴ is hydrogen a compound of formula (4') is produced and when R³ and R⁴ are both hydrogen compound of formula (4'') is produced



Scheme 14

In both schemes 13 and 14:

L is a suitable leaving group such as halo (chloro, bromo, iodo), mesyl, tosyl.

Suitable bases to deprotonate compounds of formula (17) and formula (20) include

- 10 NaH, LDA, BuLi and LHMDs. Suitable reaction conditions for a) are temperatures ranging from -78°C to 70°C and an aprotic solvent, e.g. THF under argon.

Suitable protecting groups (PG) include Boc (t-butoxycarbonyl), CBz (carbonyloxybenzyl) groups and mesyl or another alkylsulphonyl-. In the case where PG is alkylsulphonyl-, reaction of formula (16) and (17) and of formula (20) and formula (21)

- 15 directly produces a compound of formula (4).

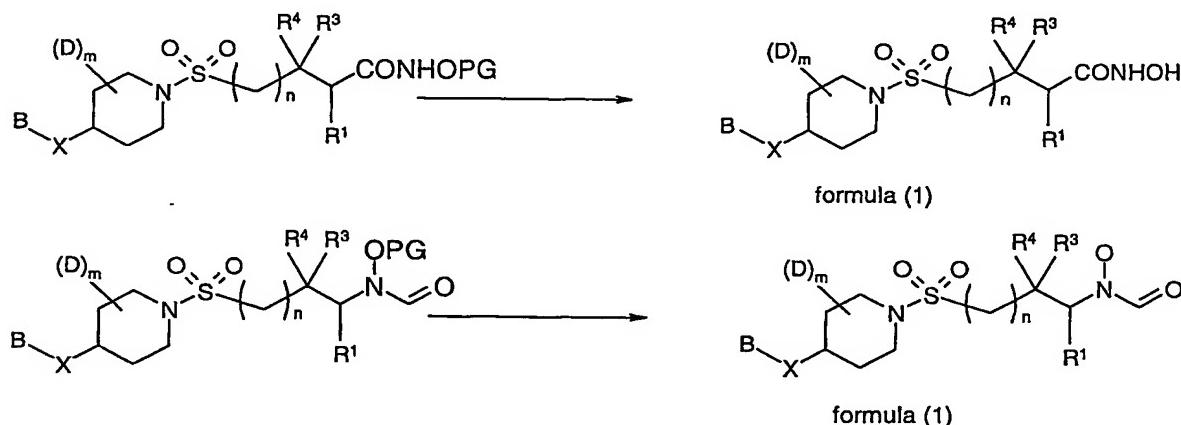
A compound of formula (18) can be converted to formula (19) by treatment with acid (Boc) or hydrogen/ palladium (CBz).

A compound of formula (19) can be converted to a compound of formula (4) by treatment with an alkylsulphonylchloride in the presence of a base such as pyridine in a solvent

- 20 such as DCM.

A compound of formula (1) can be prepared by removal of a protecting group on the zinc binding group directly. The protecting group (PG) can be benzyl- or 2,4-dimethoxybenzyl-. The former can be removed by treatment with hydrogen/ palladium and the latter by treatment with mild acid (see Tetrahedron Letters, 1998, 39(43), 7865). The required protected

- 5 hydroxamic acid or reverse hydroxamate can be obtained by using a suitably protected hydroxylamine earlier in the synthesis.



10

Scheme 15

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or

- 15 generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such
- 20 procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts
- 25 conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic

hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where 5 protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

10 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting 15 group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an 20 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

25 A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with 30 a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic
5 acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

10 As stated hereinbefore the compounds defined in the present invention possesses metalloproteinases inhibitory activity, and in particular TACE inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Isolated Enzyme Assays

15 **Matrix Metalloproteinase family including for example MMP13.**
Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) *The Biochemical Journal* 271:1544-1550 (1996)].
The purified enzyme can be used to monitor inhibitors of activity as follows: purified
20 proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl₂, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH₂ in
25 the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λ_{ex} 328nm and λ_{em} 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [Fluorescence_{plus inhibitor} - Fluorescence_{background}] divided by the [Fluorescence_{minus inhibitor} - Fluorescence_{background}].

A similar protocol can be used for other expressed and purified pro MMPs using
30 substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) *FEBS Lett.* 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNF α convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) *Nature* 370:218-220. The 5 purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH₂ in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM CaCl₂), at 26°C for 4 hours. The amount of inhibition is 10 determined as for MMP13 except λ_{ex} 485nm and λ_{em} 538nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser¹ and Pro² were double-coupled. The 15 following side chain protection strategy was employed; Ser¹(But), Gln⁵(Trityl), Arg^{8,12}(Pmc or Pbf), Ser^{9,10,11}(Trityl), Cys¹³(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) *Anal Biochem*. 20 108:156-161] which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by 25 evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

30 Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) *Osteoarthritis and Cartilage* 6:214-228; (1999) *Journal of Biological Chemistry*, 274

(10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) *Anal. Biochem.* **99**:340-345.

5 **Inhibition of metalloproteinase activity in cell/tissue based activity**

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNF α production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) *Nature* **370**:218-220. In a similar fashion

10 the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) *Biochem. J.* **321**:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

15 The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) *Cancer Research* **47**:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

20 The ability of the compounds of this invention to inhibit TNF α production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNF α . 160 μ l of heparinized (10Units/ml) human blood obtained from volunteers, was added to the plate and incubated with 20 μ l of test compound (duplicates), in RPMI1640 + bicarbonate, penicillin, streptomycin, glutamine and 1% DMSO, for 30 min at 37°C in a humidified (5%CO₂/95%air)

25 incubator, prior to addition of 20 μ l LPS (*E. coli.* 0111:B4; final concentration 10 μ g/ml). Each assay includes controls of neat blood incubated with medium alone or LPS (6 wells/plate of each). The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100 μ l) and stored in 96 well plates at -70°C before subsequent analysis for TNF α concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

5

In vivo assessmentTest as an anti-TNF agent

The ability of the compounds of this invention as *in vivo* TNF α inhibitors is assessed in the rat. Briefly, groups of female Wistar Alderley Park (AP) rats (90-100g) are dosed with 10 compound (5 rats) or drug vehicle (5 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.) 1 hour prior to lipopolysaccharide (LPS) challenge (30 μ g/rat i.v.). Sixty minutes following LPS challenge rats are anaesthetised and a terminal blood sample taken via the posterior vena cavae. Blood is allowed to clot at room temperature for 2 hours and serum samples obtained. These are stored at -20°C for TNF α ELISA and 15 compound concentration analysis.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha \text{ (Vehicle control)} - \text{Mean TNF}\alpha \text{ (Treated)}}{\text{Mean TNF}\alpha \text{ (Vehicle control)}} \times 100$$

20

Test as an anti-arthritis agent

Activity of a compound as an anti-arthritis is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates. 25

Pharmaceutical Compositions

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association 30 with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a

tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using
5 conventional excipients.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration
10 depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

15 Therefore in a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt
20 or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF α .

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of
25 treating inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in a method of treating rheumatoid arthritis, Crohn's disease and psoriasis,
30 and especially rheumatoid arthritis.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt
5 or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF α .

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in
10 the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy, in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of rheumatoid arthritis,
15 Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the
20 treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF α in a warm-blooded animal such as man.

Also provided is the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune
25 diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided in the manufacture of a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and
30 especially rheumatoid arthritis.

According to a further feature of this aspect of the invention there is provided a method of producing a metalloproteinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

5 According to a further feature of this aspect of the invention there is provided a method of producing a TACE inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a
10 method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

Also provided is a method of treating rheumatoid arthritis, Crohn's disease and
15 psoriasis, and especially rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

In addition to their use in therapeutic medicine, the compounds of formula (1) and
20 their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament
25 manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless
30 stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

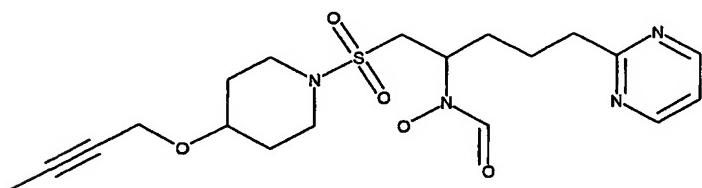
- (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;
- (iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "IsoluteTM SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industrial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where Flashmaster II is referred to, this means a UV driven automated chromatography unit supplied by Jones;
- (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (vi) when given, ¹H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD₃SOCD₃) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;
- (vii) chemical symbols have their usual meanings; SI units and symbols are used;
- (viii) solvent ratios are given in percentage by volume;
- (ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - (M+H)⁺;
- (x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A

to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - (M+H)⁺ and
 (xi) the following abbreviations are used:

5	DMSO	dimethyl sulphoxide;
	DMF	N-dimethylformamide;
	DCM	dichloromethane;
	NMP	N-methylpyrrolidinone;
	DIAD	Di-isopropylazodicarboxylate
10	LHMDS or LiHMDS	Lithium bis(trimethylsilyl)amide
	MeOH	Methanol
	RT	Room temperature
	TFA	Trifluoroacetic acid
	EtOH	ethanol
15	EtOAc	ethyl acetate.
	EDTA	ethylenediaminetetraacetic acid
	THF	tetrahydrofuran

EXAMPLE 1

20 (R/S)-1-({[4-(But-2-nyloxy)piperidin-1-yl]sulfonyl}methyl)-4-pyrimidin-2-ylbutyl(hydroxy)formamide



To a stirred solution of R/S-[1-({[4-(4-but-2-nyloxy)piperidin-1-yl]sulfonyl}methyl)-4-25 pyrimidin-2-ylbutyl]hydroxylamine (170mg, 0.43mmol) in THF (5.0ml), was added a preformed mixture of acetic anhydride (200μl, 2.1mmol) and formic acid (0.75ml). The mixture was stirred at RT for 23h. The solvents were removed by rotary evaporation, EtOAc (15ml) followed by saturated sodium hydrogen carbonate and the reaction mixture was stirred for 4h. The mixture was diluted with EtOAc (15ml) and washed with brine (10ml), dried

(Na_2SO_4) and evaporated to give a colourless film. The aqueous layer was re-extracted with DCM ($3 \times 10\text{ml}$), dried (Na_2SO_4) and combined with the previous product. This residue was purified by chromatography (Flashmaster II, eluent $0 \rightarrow 10\%$ MeOH/ DCM) to give a mixture. The mixture was redissolved in MeOH (5ml) and K_2CO_3 was added. After 16h the solution 5 was concentrated, partitioned between DCM and brine, the organic layer was dried (Na_2CO_3) and concentrated to give the title compound as a pure oil (84mg, 46%).

NMR: 8.69 (d, 2H), 8.22 & 7.90 (br s, 1H), 7.3 (t, 1H), 4.1 (q, 2H), 3.58 (m, 1H), 3.3 (m, 4H), 3.02 (m, 2H), 2.83 (m, 2H), and 1.8-1.47 (m, 11H); MS: 425.

10 The starting material was prepared as follows :

i) To solution of 4-hydroxypiperidine (20g, 198mmol) in 2M aqueous sodium hydroxide (350ml) was added methanesulphonyl chloride (25ml, 323mmol) over 10 min. The solution was stirred at ambient temperature for a further 1 h. The reaction mixture was poured into ethyl acetate (300ml) and the organic phase separated. The aqueous phase was extracted 15 with ethyl acetate ($2 \times 300\text{ml}$). The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was treated with SCX-2 resin (20g) for 15 min before filtration and evaporation to give 4-hydroxy-1-(methanesulfonyl)piperidine as a white solid, (6.62g, 19%). NMR: 3.95 (m, 1H), 3.45 (m, 2H), 3.10 (m, 2H), 2.75 (s, 3H), 1.95 (m, 2H), 1.70 (m, 2H).

20 ii) To a suspension of sodium hydride (1.5g, 37.5mmol) in DMF (350ml) was added a solution of 4-hydroxy-1-(methanesulfonyl)piperidine (6.4g, 35.7mmol) in DMF (50ml). After 20mins at RT, 1-bromo-2-butyne (3.0ml, 34.3mmol) was added rapidly. After 4h at RT water (5ml) was added and the mixture left to stand for 16h. The solvent was concentrated and the resultant brown oil was partitioned between brine (200mL) and EtOAc (200ml). The aqueous 25 phase was extracted with EtOAc ($2 \times 200\text{ml}$) and the organic layers combined. The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil which was purified by chromatography (Flashmaster II, 70g silica column, eluted with $0 \rightarrow 100\%$ Ethyl Acetate / iso-Hexane gradient) to give 4-(but-2-ynyloxy)-1-methanesulfonylpiperidine (1.8g, 22% Yield). NMR: 4.14 (q, 2H), 3.75 (m, 1H), 3.35 (m, 2H), 3.21 (m, 2H), 2.77 (s, 3H), 1.90 (m, 2H), 30 1.85 (t, 3H), 1.82 (m, 2H).

iii) To a stirred solution of the 4-(but-2-ynyloxy)-1-methanesulfonylpiperidine (461mg, 2mmol) in THF (15ml) at -15°C was added LiHMDS (4.4ml, 1.0M solution in THF,

4.4mmol). The solution was then stirred at this temperature for 30 minutes. A solution of ethyl 4-(pyrimidin-2-yl)butanoate§ (400 mg, 2.1 mmol) in THF (1 mL) was then added dropwise. The reaction was slowly allowed to warm to 5°C, then after 20mins, water (2ml) was added. The solution was partitioned between brine (20ml) and EtOAc (10ml), then the aqueous layer was re-extracted with EtOAc (10mL). The combined organic extracts were dried, (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (silica gel, 50% ethyl acetate in hexane) gave 1-{[4-(but-2-nyloxy)piperidinyl]sulfonyl}-5-(pyrimidin-2-yl)pentan-2-one as a yellow oil (286 mg, 38%). NMR: 8.67 (d, 2 H), 7.13 (t, 1 H), 4.13 (q, 2H), 3.96 (s, 2 H), 3.72 (m, 1H), 3.47 (m, 2H), 3.22 (m, 2H), 3.0 (t, 2H), 2.84 (t, 2H), 2.16 (m, 2H), 1.98 (m, 2H), 1.85 (t, 3H), 1.76 (m, 2H); MS: 380.

iv) To a stirred solution of 1-{[4-(but-2-nyloxy)piperidinyl]sulfonyl}-5-(pyrimidin-2-yl)pentan-2-one (286mg, 0.75mmol) in EtOH (5ml) was added sodium borohydride (15mgs) and the mixture stirred at RT. After 25mins the reaction mixture was concentrated and EtOAc (20ml) was added. The organic layer was washed with brine (20ml) and the aqueous fraction re-extracted with EtOAc (20ml). The combined organics were dried (Na_2SO_4) and evaporated to give R/S-1-{[4-(but-2-nyloxy)piperidinyl]sulfonyl}-5-(pyrimidin-2-yl)pentan-2-ol (286mg, 100% yield). NMR: 8.67 (d, 2 H), 7.14 (t, 1 H), 4.24 (m, 1H), 4.13 (q, 2H), 3.74 (m, 1H), 3.56 (br s, 1H), 3.42 (m, 2H), 3.24 (m, 2H), 3.02 (m, 4H), 1.85 (t, 3H), 1.81 (m, 8H); MS: 382.

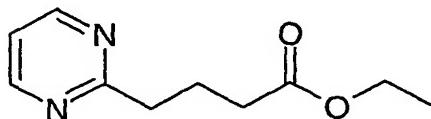
v) To a stirred solution of R/S-1-{[4-(but-2-nyloxy)piperidinyl]sulfonyl}-5-(pyrimidin-2-yl)pentan-2-ol (286mg, 0.75mmol) in DCM (5ml) was added triethylamine (260ul, 1.9mmol) followed by mesyl chloride (65uL, 0.83mmol) and the mixture stirred at RT. After 21h the reaction mixture was poured into brine, diluted with DCM (20ml) and partitioned. The organic layer was dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 10g silica column, 0→100% hexane to ethyl acetate) to give E-1-{[4-(but-2-nyloxy)piperidinyl]sulfonyl}-5-(pyrimidin-2-yl)pent-1-ene (158mg, 58% yield). NMR: 8.68 (d, 2H), 7.15 (t, 1H), 6.76(dt, 1H), 6.12 (d, 1H), 4.12 (q, 2H), 3.68 (m, 1H), 3.30 (m, 2H), 3.05 (m, 4H), 2.35 (m, 2H), 2.04 (m, 2H), 1.89 (m, 2H), 1.84 (t, 3H), 1.76 (m, 2H); MS: 364.

vi) To a stirred solution of the E-1-{{4-(but-2-nyloxy)piperidinyl}sulfonyl}-5-(pyrimidin-2-yl)pent-1-ene (158mg, 0.43mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 450μl) and the mixture stirred overnight. The mixture was poured into water (5ml) and EtOAc (15ml) and the partitioned organic layer was washed 5 with brine (5ml), dried (Na₂SO₄) and concentrated to give R/S-[1-({[4-(4-but-2-nyloxy)piperidin-1-yl]sulfonyl}methyl)-4-pyrimidin-2-ylbutyl]hydroxylamine (170mg, 100%), this was used immediately in the final step.

§Ethyl 4-(pyrimidin-2-yl)butanoate was prepared as follows:

10

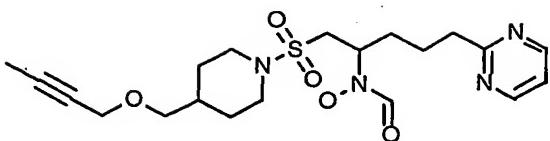
Ethyl 4-(pyrimidin-2-yl)butanoate



2-Bromopyrimidine (80g, 500mmol) was slurried in THF (400ml). An inert atmosphere was created by displacing the air atmosphere with nitrogen, followed by degassing the slurry by 15 nitrogen purging. Bis(acetonitrile)palladium (II) chloride (2.5mmol) and triphenylphosphine (7.5mmol) were charged, followed by 4-ethoxy-4-oxo-butyrlzinc bromide (0.5M in THF, approximately 600mmol) in 9 portions. The mixture was stirred until the reaction was complete at which point water was added and the solution rotary evaporated to an oil. DCM was added and this solution was washed with 1M EDTA tetrasodium salt, water and brine. 20 The DCM solution was then rotary evaporated to an oil, causing the precipitation of an impurity. This mixture was dissolved in THF, filtered to remove the impurity, then the solvent removed on a rotary evaporator affording the desired ethyl 4-(pyrimidin-2-yl)butanoate as an orange oil (95.4g, 492mmol). ¹H NMR (400MHz, d₆-DMSO) δ 8.73-8.72(d, 2H), 7.35-7.33 (t, 1H), 4.07-4.02 (q, 2H), 2.91-2.88 (t, 2H), 2.38-2.34 (t, 2H), 2.05-25 1.97 (m, 2H), 1.20-1.16 (t, 3H)

EXAMPLE 2

(R/S)-1-[(4-[(but-2-nyloxy)methyl]piperidin-1-yl)sulfonyl]methyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide



The procedure described in Example 1 was followed except that 4-(but-2-ynyloxymethyl)-1-(methanesulfonyl)piperidine(360mg, 1.47mmol) was used (synthesis described below) in place of 4-(but-2-ynyloxy)-1-methanesulfonylpiperidine to give (R/S)-1-[[(4-(but-2-

5 ynyloxy)methyl]piperidin-1-yl]sulfonylmethyl]-4-pyrimidin-2-ylbutyl(hydroxy)formamide (169mg, 0.38mmol). NMR: 8.68 (d, 2H), 8.48 (s, 0.5H), 8.04 (d, 0.5H), 7.23 (t, 0.5H), 7.19 (t, 0.5H), 4.08 (m, 2H), 3.78 (2H, m), 3.3 (m, 4H), 3.06 (m, 4H), 2.78 (m, 2H), 1.92 (m, 2H), 1.85 (t, 3H), 1.7 (m, 7H); MS: 439

10 The starting 4-(but-2-ynyloxymethyl)-1-(methanesulfonyl)piperidine was prepared as follows:

i) To a stirred solution of 4-piperidinylmethanol (2g, 17.4mmol) dissolved in DCM (250ml) was added triethylamine (6ml, 43.5mmol) followed by mesyl chloride (3.0ml, 38.2mmol). After 2.5h at RT the reaction mixture was diluted with EtOAc (500ml) and the organic layer washed with 2M HCl (100ml), NaHCO₃ (100ml), brine (100ml), dried (Na₂SO₄)

15 and evaporated to give 4-(methanesulphonyloxymethyl)-1-methanesulphonylpiperidine as an off-white solid (4.5g, 96%). NMR: 4.1 (d, 2H), 3.86 (m, 2H), 3.02 (s, 3H), 2.79 (s, 3H), 2.67 (m, 2H), 1.89 (m, 3H) and 1.43 (m, 2H).

ii) To a stirred solution of 2-butyn-1-ol (550ul, 7.4mmol) in DMF (25ml) was added

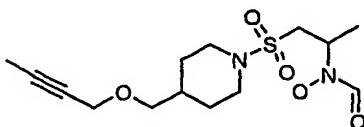
20 sodium hydride (300mg, 8.1mmol). After 90mins a solution of 4-(methanesulphonyloxymethyl)-1-methanesulphonylpiperidine (2.0g, 7.4mmol) in DMF (30ml) was added. After 2h stirring at RT water (5ml) was added and the mixture concentrated to a brown oil. This was partitioned between EtOAc (100ml) and brine (150ml). The aqueous layers were re-extracted with EtOAc (2x50ml) and the combined organic

25 fractions were dried (Na₂SO₄), evaporated and purified by chromatography (Flashmaster II, 50g silica, 50→100% hexane to ethyl acetate) to give 4-(but-2-ynyloxymethyl)-1-(methanesulfonyl)piperidine(680mg, 2.8mmol, 37%). NMR: 4.07 (q, 2H), 3.81 (br m, 2H), 3.35 (d, 2H), 2.76 (s, 3H), 2.64 (m, 2H), 1.8 (m, 5H), 1.71 (m, 1H), 1.35 (m, 2H).

EXAMPLE 3

(R/S)-2-({4-[(But-2-nyloxy)methyl]piperidin-1-yl}sulfonyl)-1-methylethyl(hydroxy)formamide

5



To a stirred solution of R/S-2-{[4-(but-2-nyloxy)methyl]piperidin-1-yl}sulfonyl}-1-methylethylhydroxylamine (112mg, 0.37mmol) in THF (5.0ml), was added a preformed mixture of acetic anhydride (200 μ l, 2.1mmol) and formic acid (0.75ml). The mixture was stirred at RT overnight. The solvents were removed by rotary evaporation, EtOAc (10ml) followed by saturated sodium hydrogen carbonate and the reaction mixture was stirred for 2h. The mixture was washed with brine (10ml), dried (Na_2SO_4) and evaporated to give a pale yellow oil. This residue was purified by chromatography (Flashmaster II, eluent 0 \rightarrow 60% EtOAc / Dichloromethane) to give (R/S)-2-({4-[(but-2-nyloxy)methyl]piperidin-1-yl}sulfonyl)-1-methylethyl(hydroxy)formamide (75mg, 0.22mmol). NMR: 7.96 (s, 1H), 4.36 (m, 1H), 4.08 (q, 2H), 3.77 (m, 2H), 3.47 (dd, 1H), 3.34 (d, 2H), 2.90 (dd, 2H), 2.75 (m, 2H), 1.85 (t, 3H), 1.82 (m, 2H), 1.74 (m, 1H), 1.48 (d, 3H), 1.34 (m, 2H); MS: 333.

The starting material was prepared as follows:

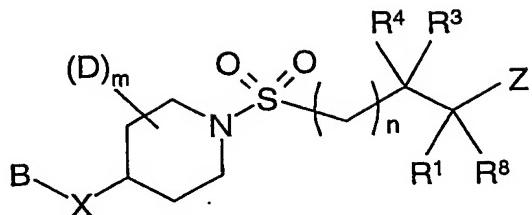
i) To a stirred solution of the 4-(but-2-nyloxy)methyl)-1-methanesulfonylpiperidine (prepared above) (320mg, 1.3mmol) in THF (10ml) at -17°C under argon was added LiHMDS (2.8ml, 1.0M solution in THF, 2.8mmol). The solution was then stirred at this temperature for 30 minutes. A solution of diethylchlorophosphate (190 μ L, 1.31mmol) was then added and the reaction mixture stirred at 0°C for a further 50mins. Acetaldehyde (100 μ L, 1.8mmol) was then added. After 15h the reaction was quenched with saturated ammonium chloride (10ml). The organic phase was separated and the aqueous layer extracted with EtOAc (30ml). The combined organics were combined, washed with brine (10ml), dried (Na_2SO_4), concentrated and chromatographed (Flashmaster II, 50g silica, 50 \rightarrow 100% hexane to ethyl acetate) to give E/Z-{1-[4-(but-2-nyloxy)methyl]piperidin-1-yl}sulfonyl}prop-1-ene as a yellow oil (100 mg, 0.37mmol). MS: 272.

ii) To a stirred solution of the E/Z-{1-[4-(4-but-2-ynylloxymethyl)piperidin-1-yl]sulfonyl}prop-1-ene (100mg, 0.37mmol) in THF (5ml) under argon was added hydroxylamine (50% solution in water, 450μl) and the mixture stirred over the weekend. The mixture was poured into water (5ml) and EtOAc (15ml) and the partitioned organic layer was washed with brine (5ml), dried (Na_2SO_4) and concentrated to give R/S-2-{{[4-(but-2-ynylloxymethyl)piperidin-1-yl]sulfonyl}-1-methylethylhydroxylamine (112mg, 0.37mmol).
5 This was used immediately in the final step.

CLAIMS:

What we claim is :-

1. A compound of formula (1):



formula (1)

5

wherein Z is selected from $-\text{CONR}^{15}\text{OH}$ and $-\text{N(OH)CHO}$;

R^{15} is hydrogen or $\text{C}_{1-3}\text{alkyl}$;

10

wherein R^1 is hydrogen or a group selected from $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, $\text{C}_{3-7}\text{cycloalkyl}$, $\text{C}_{5-7}\text{cycloalkenyl}$, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{2-4}\text{alkenyl}$, $\text{C}_{2-4}\text{alkynyl}$, $\text{C}_{3-6}\text{cycloalkyl}$

15 (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $\text{C}_{1-4}\text{alkoxycarbonyl}$, $-\text{OR}^5$, $-\text{SR}^2$, $-\text{SOR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{COR}^2$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^5\text{R}^6$, $-\text{NR}^{16}\text{COR}^5$, $-\text{SO}_2\text{NR}^5\text{R}^6$ and $-\text{NR}^{16}\text{SO}_2\text{R}^2$;

20 R^{16} is hydrogen or $\text{C}_{1-3}\text{alkyl}$;

R^{17} is selected from halo, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$ and $\text{C}_{1-6}\text{alkoxy}$;

25 R^2 is group selected from $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, $\text{C}_{5-7}\text{cycloalkenyl}$, heterocycloalkyl, aryl, heteroaryl, aryl $\text{C}_{1-4}\text{alkyl}$ and heteroaryl $\text{C}_{1-4}\text{alkyl}$ where the group is optionally substituted by one or more halo;

R^5 is hydrogen or a group selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-7} cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, aryl C_{1-4} alkyl and heteroaryl C_{1-4} alkyl where the group is optionally substituted by one or more halo;

5 R^6 is hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

or R^5 and R^6 together with the nitrogen to which they are attached form a heterocyclic 4- to 7-membered ring;

10 wherein R^8 is hydrogen or a group selected from C_{1-6} alkyl, C_{3-7} cycloalkyl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethoxy and C_{1-4} alkyl;

or R^1 and R^8 together form a carbocyclic or saturated heterocyclic 3- to 6-membered ring;

15

wherein R^3 and R^4 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-7} cycloalkenyl, heterocyclyl, aryl or heteroaryl;

wherein n is 0 or 1;

20

wherein m is 0 or 1;

wherein D is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl or fluoro;

25 wherein X is $-(CR^9R^{10})-Q-(CR^{11}R^{12})u-$ where u is 0 or 1;

Q is O, S, SO or SO_2 ;

R^9 , R^{10} , R^{11} and R^{12} are independently selected from hydrogen, C_{1-4} alkyl and C_{3-6} cycloalkyl;

30

wherein B is C_{2-4} alkenyl or C_{2-4} alkynyl, each being optionally independently substituted by a group selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heterocyclyl whereby the group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl,

trifluoromethoxy, $-\text{CONHR}^{13}$, $-\text{CONHR}^{13}\text{R}^{14}$, $-\text{SO}_2\text{R}^{13}$, $-\text{SO}_2\text{NHR}^{13}$, $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $-\text{NHSO}_2\text{R}^{13}$, $\text{C}_{1-4}\text{alkyl}$ and $\text{C}_{1-4}\text{alkoxy}$.

R^{13} and R^{14} are independently hydrogen, $\text{C}_{1-4}\text{alkyl}$ or $\text{C}_{3-5}\text{cycloalkyl}$;

5

or R^{13} and R^{14} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring;

or a pharmaceutically acceptable salt thereof.

10

2. A compound according to Claim 1, for use as a medicament.

3. The use of a compound according to Claim 1 in the manufacture of a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes.

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4. The use of a compound according to Claim 1 in the manufacture of a medicament in the treatment of a disease condition mediated $\text{TNF}\alpha$.

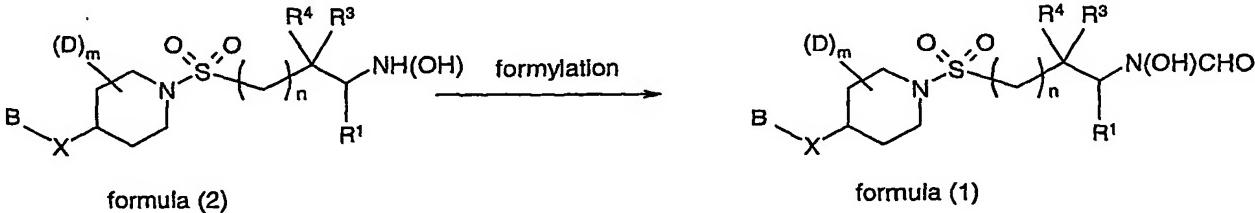
5. A pharmaceutical composition comprising a compound according to Claim 1; and a

20 pharmaceutically-acceptable diluent or carrier.

6. A process for preparing a compound according to Claim wherein Z is $-\text{N}(\text{OH})\text{CHO}$, comprising the steps of:

a) converting a hydroxylamine of formula (2) into a compound of formula (1);

25



and thereafter if necessary:

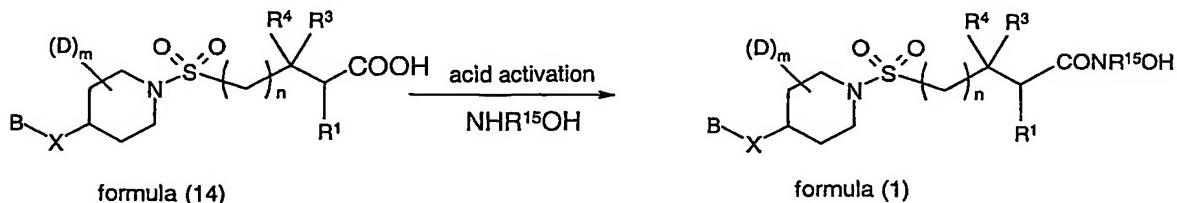
i) converting a compound of the formula (1) into another compound of the formula (1);

30 ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

7. A process for preparing a compound according to Claim 1 wherein Z is $-\text{CONR}^{15}\text{OH}$ comprising the steps of:

- 5 a) converting an acid of formula (14) into a compound of formula (1);



and thereafter if necessary:

- i) converting a compound of the formula (1) into another compound of the formula (1);
 10 ii) removing any protecting groups;
 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

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